

Ecological model of solid tumor tissue with bifidobacteria

A part of human's tissue can be regarded as a miniature ecosystem. Tumor cells can be thought as a kind of invasive species and the normal somatic cells can be viewed as the original species of the ecosystem. When the ecological system is healthy, the number of tumor cells will be limited in a low range by the body's immune system and somatic cells have a survival advantage comparing with tumor cells. So, if there is a small amount of tumor cells, they will be eliminated through the competition with the somatic cell. However, when the body ecosystem is in a bad condition (such as HIV/AIDS patients), the immune system is compromised, and the carrying capacity of tumor cells in the body ecosystem is greatly increased. Therefore, tumor cells have a better survival advantage than somatic cells under this condition. As a result, somatic cells will be suppressed, and the body will be sick.

Based on the hypothesis above, the quantitative relation between tumor cells and somatic cells can be simulate by the following mathematical model. Besides, we have also established a differential equation to evaluate the population change of solid tumor cells and somatic cells when we introduce bifidobacterium as a predator in the ecosystem to kill solid tumor cells. The differential equations are based on the Lotka–Volterra equations and Holling models.

In this article, we first introduce four basic models, and gradually establish our models to estimate the population of the three kinds of cells and show the curve of the population change with time.

1. The basic relationship models of population

There are four basic population models that will be used in our modeling: Malthus Model, Logistic Model, Lotka-Volterra Model, Volterra Predation Relation Model. Among them, Malthus Model and Logistic Model are single-species population growth model, established by Thomas Robert Malthus and Pierre François Verhulst respectively. Lotka-Volterra Model and Volterra Predation Relation Model are multiple-species population model.

1.1 Malthus Model

Set the natural growth rate r of a species as constant, time t as a variable. The population quantity of the species is $x(t)$. Consider the change of $x(t)$ at time t to $t+\Delta t$, there exists $x(t+\Delta t) - x(t) = r\Delta tx(t)$. Thus the differential equation of $x(t)$ is:

$$\begin{cases} \frac{dx}{dt} = rx \\ x(0) = x_0 \end{cases} \quad (1)$$

Set the community biomass at initial time as x_0 , then $x(0) = x_0$. Solving this equation:
 $x(t) = x_0 e^{rt}$

Thus the population growth following the index law.

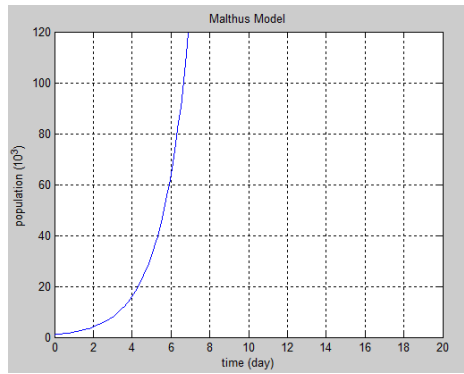


Figure1: Mathus Model

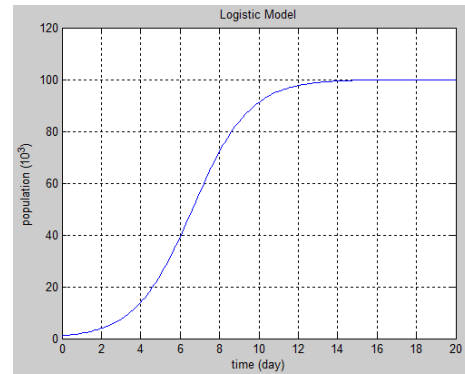


Figure2: Logistic Model

1.2 Logistic Model

Considering the factors of competition between members of different organisms due to the limiting life place, food and living space, Logistic model adds a limiting factor, $(1 - \frac{x}{N})$, in the differential equation, and the carrying capacity in the ecosystem is N . The group initial natural growth rate, r , will declines when the population grows. Once the biological moment grows to N , the group will stop growing. Differential equations:

$$\begin{cases} \frac{dx}{dt} = r(1 - \frac{x}{N})x \\ x(0) = x_0 \end{cases} \quad (2)$$

$\frac{x}{N}$ can be understood as occupied resource, and $(1 - \frac{x}{N})$ can be understood as available resource.

The solution of the equation above:

$$x(t) = \frac{Nx_0 e^{rt}}{x_0(e^{rt}-1)+N}$$

1.3 Lotka-Volterra Model

In the 40 s of the 20th century, on the basis of the single-species model, the Lotka-Volterra double population competition model was put forward by Lotka and Volterra. The model sets the following variables and parameters:

x_1, x_2 : the population quantity of species1 and species2

N_1, N_2 : the environmental capacity of species1 and species2

r_1, r_2 : the natural growth rate of species1 and species2

m_1 : the coefficient competition of species2 to species1, means the resource used by one individual of species2 amount to m_1 individuals of species1

m_2 : the coefficient competition of species1 to species2, means the resource used by one individual of species1 amount to m_2 individuals of species2

When the two species compete and use the same resource, the factor $\frac{x}{N}$ should add the factor of the resource occupation of competitive species. The differential equation:

$$\begin{cases} x_1'(t) = r_1 x_1 \left(1 - \frac{x_1 + m_1 x_2}{N_1}\right) \\ x_2'(t) = r_2 x_2 \left(1 - \frac{x_2 + m_2 x_1}{N_2}\right) \end{cases} \quad (3)$$

The root of differential equation has some feature:

Setting the initial point as $t = 0$, then:

(1) When $m_1 N_2 < N_1$ and $m_2 N_1 < N_2$, whatever the initial point is, when $t \rightarrow \infty$, then

root $\rightarrow \left(\frac{N_2 - m_2 N_1}{1 - m_1 m_2}, \frac{N_1 - m_1 N_2}{1 - m_1 m_2} \right)$, which means two species both exists. (the arrow means approach to)

(2) When $m_1 N_2 < N_1$ and $m_2 N_1 > N_2$, whatever the initial point is, when $t \rightarrow \infty$, then root $\rightarrow (N_1, 0)$,

which means the second one will be weed out ;

(3) When $N_2 > N_1$ and $m_2 N_1 < N_2$, whatever the initial point is, when $t \rightarrow \infty$, then root $\rightarrow (0, N_2)$,

which means the first one will be weed out ;

(4) When $m_1 N_2 > N_1$ and $m_2 N_1 > N_2$, when $t \rightarrow \infty$, then root $\rightarrow (0, N_2)$ or $(N_1, 0)$, which balance point will the root tend to be, is determined by the initial condition.

1.4 Volterra Predation Relation Model

Volterra etc. not only put forward the competition model, but also raising the predator-prey model. The model sets the following variables and parameters:

x: the population quantity of prey

y: the population quantity of predation

r: the inherent growth rate of prey

d: the inherent death rate of predation

a: the capacity coefficient of predation grabbing the prey

b: the capacity coefficient of prey supporting the predation

Differential equation:

$$\begin{cases} x'(t) = x(r - ay) \\ y'(t) = y(-d + bx) \end{cases} \quad (4)$$

The solutions of the equation are two periodic functions.

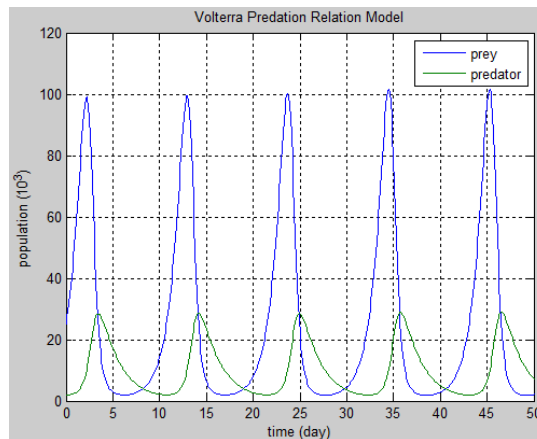


Figure3: Volterra Predation Relation Model

2. The somatic cells - tumor cells relation model

Considering the tumor cells acts as an invasive species in the ecosystem, and compete with somatic cell for resources, so the competition model is an appropriate model to simulate the relationship between tumor cells and somatic cells. We set x_1 as the population of tumor cells, x_3 as the population of somatic cells. The rest of the parameters settings:

N_1 : the environmental capacity of tumor cells in the tissue

N_2 : the environmental capacity of bifidobacteria in the tissue

N_3 : the environmental capacity of somatic cells in the tissue

m_1 : the coefficient competition of somatic cells to tumor cells

m_3 : the coefficient competition of tumor cells to somatic cells

r_1 : the natural growth rate of tumor cells

r_3 : the natural growth rate of somatic cells

$$\begin{cases} x_1'(t) = r_1 x_1 \left(1 - \frac{x_1 + m_1 x_3}{N_1}\right) \\ x_3'(t) = r_3 x_3 \left(1 - \frac{x_3 + m_3 x_1}{N_3}\right) \end{cases} \quad (5)$$

When ecological system is healthy, the immune system can limit environmental capacity of tumor cell in a low scope (N_1 is very low). Meeting the conditions $m_1 N_3 > N_1$ and $m_3 N_1 < N_3$ (condition 3 in Lotka-Volterra Model), the somatic cells have a huge survival advantage than tumor cell. As time increases, the tumor will be eliminated. But when the body ecosystem is defected and the body's immune system is weak, the tumor cells' allowing maximum survival number will greatly increase and then somatic cells will be eliminated ($m_1 N_3 < N_1$ and $m_3 N_1 > N_3$ condition 2 in Lotka-Volterra Model). Then, the solid tumor will grow in the tissue ecosystem.

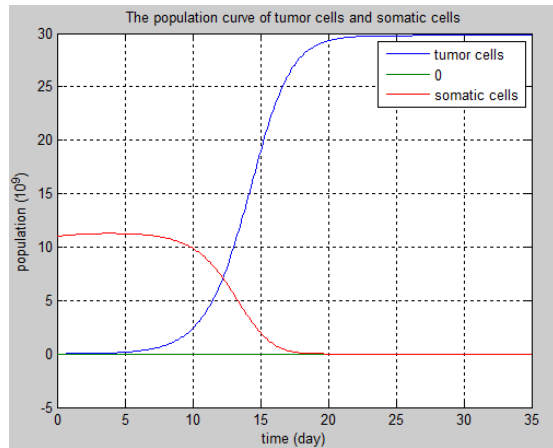


Figure4: The population change when the body's immune system is weak. $m_1 N_3 < N_1$ and $m_3 N_1 > N_3$. Solid tumor cells gradually increase to the environmental capacity N_1 , and somatic cells' population gradually declines to zero. This model is based on the Lotka-Volterra Model, and explains how the solid tumor grow when tumor cells compete with somatic cells.

3. Bifidobacteria-tumor cells relation model

3.1 Basic predator-prey relation model

When bifidobacteria target tumor tissues, for one thing, bifidobacteria secrete apoptin to promote tumor cells apoptosis. So for the tumor cells, bifidobacterium is equivalent to a predator in the tissue ecosystem; for another thing, bifidobacterium is strictly anaerobic bacterium, when tumor cells' population decreases and then the oxygen concentration increases, the growth of bifidobacterium is suppressed and it will die gradually. So the relationship between the

bifidobacteria and the tumor cells seems to be a parasitic relationship.

Variables and parameters set as follows:

x_1 : the population of tumor cells

x_2 : the population of bifidobacteria

r_1 : the natural growth rate of tumor cells

r_2 : the natural growth rate of bifidobacteria in best hypoxia condition

R_2 : the death rate of bifidobacteria in nontumorous condition (the oxygen concentration is high)

N_1 : the environmental capacity of tumor cells

N_2 : the environmental capacity of bifidobacteria

n_1 : the coefficient competition of bifidobacteria to tumor cells

n_2 : the coefficient competition of tumor cells to bifidobacteria

a : the predation coefficient of bifidobacteria to tumor cells (related to the ability of apoptin to kill tumor cells)

b : unit adjust factor (adjustment for unit difference, take 1×10^9 as unit)

Considering the tumor cell population decline will cause the oxygen concentration increasing and changing the natural growth rate of the bifidobacteria, the number of tumor cells and the natural growth rate of the bifidobacteria can be roughly associated with function image as follows.

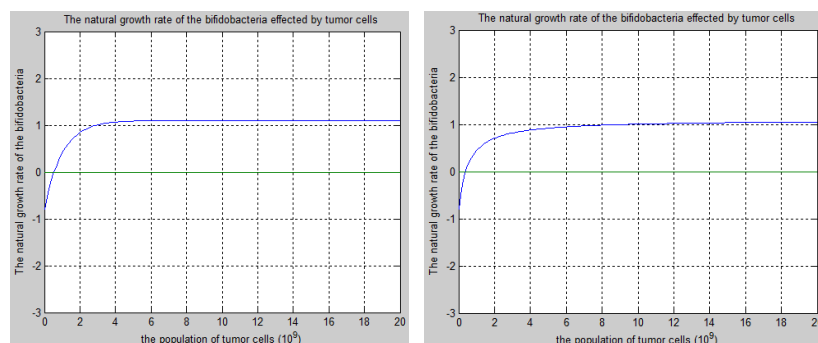


Figure5: The natural growth rate of the bifidobacteria change with the population of solid tumor cells. When the population of solid tumor cells is high, the concentration of oxygen will be low, and the natural growth rate of the bifidobacteria will be high.

The basic functions, which images are consistent to the images above, are separated into two kinds, one is exponential function, and the other is inverse proportional function. Considering the exponential function changes faster at the beginning, which is more accordant to the actual situation, we establish the exponential function model as follows:

$$r = r_2 - e^{-\frac{x_1}{b} + \ln(r_2 + R_2)}$$

r : the natural growth rate of bifidobacteria

When tumor cells amount $x_1 \rightarrow \infty$, then $r \rightarrow r_2$

When tumor cells amount $x_1 \rightarrow 0$, then $r \rightarrow R_2$

Then we establish the Bifidobacterium-tumor model based on the Volterra Predation Relation Model.

The differential equation of bifidobacteria and tumor cells:

$$\begin{cases} x_1'(t) = x_1 \left[r_1 \left(1 - \frac{x_1 + n_1 x_2}{N_1} \right) - a x_2 \right] \\ x_2'(t) = x_2 \left(r_2 - e^{-\frac{x_1}{b} + \ln(r_2 + R_2)} \right) \left(1 - \frac{x_2 + n_2 x_1}{N_2} \right) \end{cases} \quad (6)$$

In the first equation there are environmental resistance $1 - \frac{n_1 x_2}{N_1}$ and predation factor ax_2 ;

In the second equation there are environmental resistance $1 - \frac{n_2 x_1}{N_2}$ and oxygen concentration

restriction factor $r_2 - e^{-\frac{x_1}{b} + \ln(r_2 + R_2)}$

With the appropriate parameter values and the initial point taking in, the image:

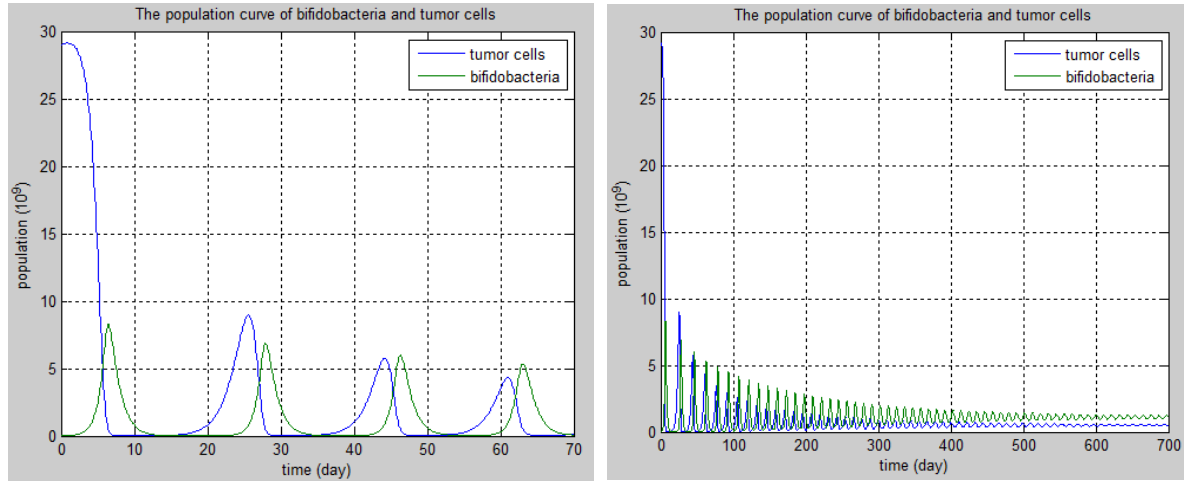


Figure6: The population curve of bifidobacteria and tumor cells based on Volterra Predation Relation Model.

It can be viewed in figure6, the tumor cells number (high at $t=0$) and bifidobacteria population (low at $t=0$) is a gradually reducing amplitude volatile relationship. When time increases, the population of both kinds of cells approaching to a lower value. So, if the parameter values are fit, bifidobacteria can limit tumor cells in a low level.

3.2 Prey Dependence Functional Reacting Model

For predators, when the population of prey increases, predator will get more food in unit time and eventually tend to be a maximum value. Volterra Predation Relation Model does not reflect this point. In order to fix this deficiency, Holling etc. put forward Prey Dependence Functional Reacting Model at 1965. Considering tumor cells can not supply nutrition to bifidobacteria as true preys do, we select Holling II Type Functional Reacting Model to reflect the saturation condition of tumor cells. It means when the population of tumor cells is low, bifidobacteria will kill more tumor cells in unit time when the population of tumor cells increase, but when the population of tumor cells is at a high level, the number of tumor cells killed by bifidobacteria in unit time will approach to a maximum value.

So, ax_1x_2 changes into $\frac{ax_1x_2}{b+x_1}$, and differential equations ⑥ changes to be the following equations:

$$\begin{cases} x_1'(t) = x_1 r_1 \left(1 - \frac{x_1 + n_1 x_2}{N_1} \right) - \frac{ax_1 x_2}{b + x_1} \\ x_2'(t) = x_2 \left(r_2 - e^{-\frac{x_1}{b} + \ln(r_2 + R_2)} \right) \left(1 - \frac{x_2 + n_2 x_1}{N_2} \right) \end{cases} \quad (7)$$

With the appropriate parameter values and the initial point taking in, the image:

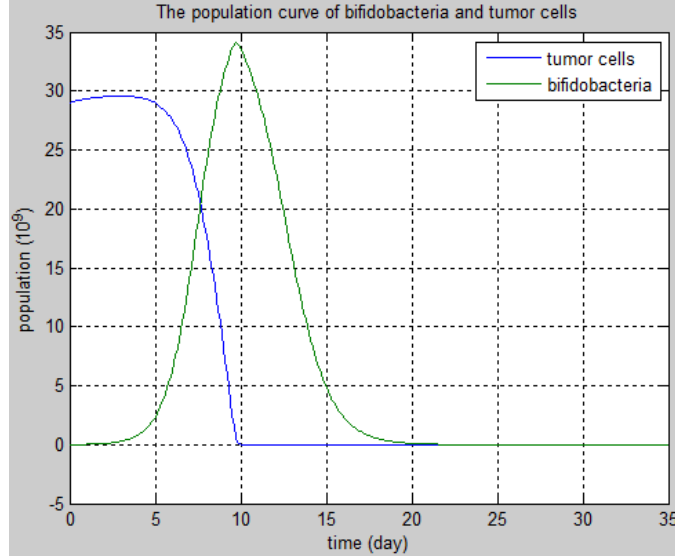


Figure7: The population curve of bifidobacteria and tumor cells based on Holling II Type Functional Reacting Model.

In figure 7, the tumor cells slowly increase at early time. As the population of bifidobacteria rising, the population of tumor cells declined sharply, then the population of bifidobacteria goes down after it get to the maximum value. Finally, the populations of bifidobacteria and tumor cells reach to zero. In this model, with the appropriate parameter, bifidobacteria can reduce the amount of tumor cells, and the population of bifidobacteria gradually drop to zero.

4. Tumor cell - bifidobacterium-somatic cell model

We consider the tumor tissue as a homogeneous environment, there exists a great number of tumor cells and a small number of somatic cells, when a few of bifidobacteria parasitize in tumor tissue, the relationships of these three kinds of cells show as follows.

- (1) Tumor cells compete with somatic cells, and bifidobacteria prey on tumor cells.
- (2) Bifidobacteria compete with somatic cells, restricted by oxygen.
- (3) Somatic cells compete with tumor cells and bifidobacteria.

Assuming the somatic cells can multiply, setting the natural growth rate as r_3 .

The differential equation based on Holling II Type Functional Reacting Model:

$$\begin{cases} x_1'(t) = x_1 r_1 \left(1 - \frac{x_1 + n_1 x_2 + m_1 x_3}{N_1} \right) - \frac{a x_1 x_2}{b + x_1} \\ x_2'(t) = x_2 \left(r_2 - e^{-\frac{x_1}{b} + \ln(r_2 + R_2)} \right) \left(1 - \frac{x_2 + n_2 x_1 + L_2 x_3}{N_2} \right) \\ x_3'(t) = r_3 x_3 \left(1 - \frac{x_3 + m_3 x_1 + L_3 x_2}{N_3} \right) \end{cases}$$

⑧

With the appropriate parameter values and the initial point taking in, the image shows as follows.

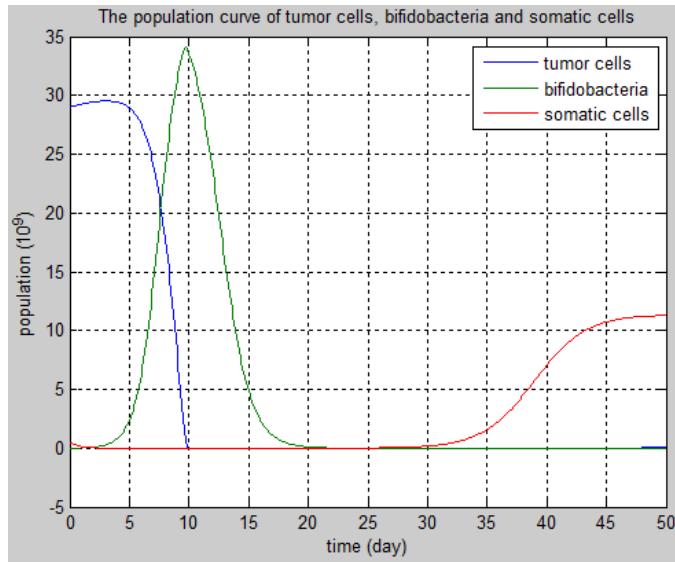


Figure8: The population curve of tumor cells, bifidobacteria and somatic cells. Under suitable parameters, the population of tumor cells decreases from a high level while the population of bifidobacteria goes up and then decreases and tend to zero. The population of somatic cells increases after the

population of tumor cells and bifidobacteria come to zero. This model shows bifidobacteria can be used to kill the tumor cells and bifidobacteria will not leave for a long time in the tissue after tumor cells die off.

From the model, tumor cells are killed by bifidobacteria and the population of tumor cells decreases. Then the growth of bifidobacteria will be restrained for rising of oxygen concentration. When the population of competitors declines and the improvement of the environment, the population of somatic cells will constantly increase, finally recover to normal level. So in this model, bifidobacteria can be used to kill the tumor cells and they will not stay for a long time in the tissue after tumor cells die off.

Parameters List

t : time

x_1 : the population of tumor cells

x_2 : the population of bifidobacteria

x_3 : the population of somatic cells

r_1 : the natural growth rate of tumor cells

r_2 : the natural growth rate of bifidobacteria in best hypoxia condition

r_3 : the natural growth rate of somatic cells

R_2 : the death rate of bifidobacteria in nontumorous condition (the oxygen concentration is high)

N_1 : the environmental capacity of tumor cells

N_2 : the environmental capacity of bifidobacteria

N_3 : the environmental capacity of somatic cells

m_1 : the coefficient competition of somatic cells to tumor cells

n_1 : the coefficient competition of bifidobacteria to tumor cells

n_2 : the coefficient competition of tumor cells to bifidobacteria

L_2 : the coefficient competition of somatic cells to bifidobacteria

L_3 : the coefficient competition of bifidobacteria to somatic cells

m_3 : the coefficient competition of tumor cells to somatic cells

a : the predation coefficient of bifidobacteria to tumor cells (related to the ability of apoptin to kill tumor cells)

b : unit adjust factor (adjustment for unit difference, take 1×10^9 as unit)

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